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14. ABSTRACT

. We have spent the first year getting IRB approval and meeting with other experts in high altitude physiology and medicine to ensure that our research approach is solid. The following organizations have approved our protocol: a) Sacred Heart Medical Center IRB, the review board for Oregon Heart and Vascular Institute; b) Oregon Public Health and Safety (OPHS) and the University of Oregon Radiation Safety Committee; c) The State of Oregon; d) The University of Oregon IRB; e) The Department of Defense IRB. Robert Roach, Ph.D., Director of the Altitude Center at the University of Colorado School of Medicine provided us with an enormous amount of insight and assistance in ensuring that we will succeed in our aims. The hyperbaric chamber was set up and potential subjects have begun to be recruited. Two subjects have completed part of the protocol. The data thus far support our hypothesis that individuals who are susceptible to Acute Mountain Sickness (AMS) will have significantly greater amounts of shunt in hypoxia and/or have an intracardiac shunt such as a PFO and thus a greater degree of arterial hypoxemia than individuals who are not AMS susceptible.

15. SUBJECT TERMS- Acute Mountain Sickness Susceptibility, intrapulmonary shunt, intracardiac shunt

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Introduction:
Previous research has shown that some individuals are more susceptible to acute mountain sickness (AMS) than others and that the development of arterial hypoxemia hours before the onset of AMS can predict with great accuracy, who is will get sick upon further ascent (1, 2). However, why some people develop greater degrees of hypoxemia than others remains unresolved. We proposed that greater degrees of intrapulmonary and intracardiac shunting (through patent foramen ovale(PFO)) are responsible for the greater degree of arterial hypoxemia in AMS susceptible subjects compared to AMS resistant subjects. In this study we aim to identify which subjects will develop a greater degree of arterial hypoxemia in hypoxic environments in advance of ascent to high altitude. To do this we will evaluate hypoxia-induced intrapulmonary and intracardiac shunt using saline contrast echocardiography to determine bubble/shunt scores. We will also use nuclear medicine imaging to determine shunt fractions following acute exposures to hypoxia to correlate bubbles scores with shunt fractions. We will also determine which subjects develop AMS by exposing them to 10 hrs of 11.5% oxygen in an environmental chamber. This will allow us to link AMS score (susceptibility to AMS) to intrapulmonary and intracardiac bubble scores/shunt fractions and thus be able to predict who will get sick before ascent to high altitude using non-invasive, inexpensive ultrasound technology.

Body:
For **Task #1** "Hypoxia-induced shunt in subjects without PFO (PFO-), 30 min exposure" 10 PFO- subjects have completed saline contrast echocardiography while breathing hypoxic gas mixtures.

For **Task #2** "10 hr hypoxic exposure and AMS susceptibility (PFO- subjects)" which is proposed to evaluate an individual's susceptibility to AMS using a 10 hr hypoxic exposure of 11.5% (~4,760 m), the 9 PFO- subjects that have completed the acute exposure have also completed the 10 hr exposure. Four subjects were classified as AMS+ and 5 as AMS- (Fig. 1, solid circles).

For **Task # 2.2** "Determine if shunt predicts AMS susceptibility" we have looked at each of the PFO- subject's bubble score after breathing an FIO_2=0.14(~ 3,320 m) for 30 min in relation to AMS susceptibility. The 2 PFO- subjects that achieved a bubble score of 3 after 30 min were classified as AMS susceptible, whereas the 5 of the PFO- subjects who achieved a bubble score of 2 or less after 30 min were classified as AMS resistant. One PFO- subject, who achieved a bubble score of 2 and one PFO- subject who achieved a bubble score of 0 were classified as AMS susceptible (Fig. 1).

Based on our current data we can predict with 78% accuracy whether PFO- subjects who have completed the saline contrast echocardiography while breathing an FIO_2=0.14, will be susceptible or resistant to developing AMS after 10 hr hypoxic exposure.

For **Task #3** "Hypoxia-induced shunt during 30 min exposure, & AMS susceptibility after 10hr exposure (PFO+)" 15 PFO+ subjects have completed saline contrast echocardiography while breathing hypoxic gas mixtures for 30 min and all of these subjects have also completed the 10 hr exposure (FIO_2=0.115) to determine AMS susceptibility. Seven PFO+ subjects were classified as AMS susceptible, while the other eight PFO+ were classified as AMS resistant. Interestingly, all four PFO+ subjects that demonstrated intracardiac shunting without a Valsalva maneuver were classified as AMS susceptible, while PFO+ subjects that are AMS resistant only demonstrated intracardiac shunting upon Valsalva maneuver.

We expect subjects that are PFO+ to demonstrate some level of hypoxia-induced intrapulmonary shunt but we have also looked at bubble score after breathing an FIO_2=0.14 for 30 min to determine if this can predict AMS susceptibility in PFO+ subjects as well. Six out of seven PFO+ subjects that were classified as AMS susceptible demonstrated a bubble score of 3 or greater after breathing an FIO_2=0.14 for 30 min, while only one PFO+ subject achieved a bubble score of 2. Six out of eight PFO+ subjects that were classified as AMS resistant achieved bubble scores of 2 or less at this time point and two achieved a bubble score of 3 (Fig. 1).

Based on our current data we can predict with 80% accuracy whether PFO+ subjects who have completed the saline contrast echocardiography while breathing an FIO_2=0.14, will be susceptible or resistant to developing AMS after 10 hr hypoxic exposure. This prediction accuracy increases to 100% when only considering subjects determined to have non-Valsalva induced PFOs.

In summary, a total of 24 subjects (9 PFO- & 15 PFO+) have completed a 30 min hypoxic exposure at FIO_2=0.14 and have also completed the 10 hr exposure (FIO_2=0.115). Of these, 11 subjects were classified as AMS+ (4 PFO-, 7 PFO+) and 13 were classified as AMS- (5 PFO-, 8 PFO+). Thus far, bubble scores achieved after breathing an FIO_2=0.14 for 30 min were predictive of AMS susceptibility in 79% of all subjects, such that subjects (PFO+ & PFO-) with a bubble score

of 3 or more at this time point were AMS susceptible while subjects (PFO- & PFO+) with a bubble score of 2 or less at this time point were AMS resistant.

Figure 2 shows the shunt score each individual achieved after breathing an FIO_2=0.14 for 30 minutes vs. the highest LLS score they achieved while breathing 11.5% O_2 for 10hrs in the environmental chamber. AMS classification was determined using overall LLS scores and headache severity. AMS susceptible subjects achieved a LLS score of 3 or greater with at least a moderate headache at one or more of the measurement time points throughout the 10 hr exposure to 11.5% O_2, whereas AMS resistant subjects always had a LLS score of three or less with mild or no headache.

Although we have previously focused on bubble scores achieved after breathing a FIO_2=0.14 for 30 min, we have recently determined that breathing an FIO_2=0.14 for only 15 minutes provides a very similar prediction rate. With the current 24 subjects, achieving a bubble score of 3 or more at this time point predicts that the subject will be AMS susceptible and a score of 2 or less predicts that the subject will be AMS resistant with 83% accuracy (Fig. 3).

We have recently hired a post-doctoral fellow (J.J. Duke, PhD) to facilitate the completion of **Task #1.3** "Quantify shunt during hypoxic exposure (14% and 11.5% O_2) with SPECT-CT" in PFO- subjects and **Task #3.2** "Quantify shunt during hypoxic exposure (14% and 11.5% O_2) with SPECT-CT" in PFO+ subjects. Beginning data collection on this aim/task has been delayed due to the development and refinement of the nuclear imaging techniques. However, our efforts spent on the refinements have been well spent, resulting in a much better process. JJ Duke is now trained in this technique and will begin collecting data on these aims within the next quarter.

No milestones are currently projected to be completed by the end of Year 2. However, there are several Milestones projected to be completed half-way through Year #3. These Milestones include: Milestones #2, #4, #6. We are currently on track to complete Milestones #2, #4, #5 (early completion), #6 and #8 (early completion) by Year 2.5. Milestones #3 & #7 are projected to be completed by the end of Year #3 and we anticipate those to be completed by that time. In Summary we are on track to complete all Milestones in a timely fashion.

Lastly, we initiated collaboration with Robert Roach, PhD at the University of Colorado, Denver to determine if the chamber data we have collected on predicting AMS susceptibility is also applicable to the prediction of AMS susceptibility in field studies. We collected these data over the summer as part of an ongoing study that Dr. Roach was directing. We are still in the data entry stage of this collaboration but we expect that these data will further validate our findings and further increase the value of our findings for the Military.

Key Research Accomplishments:

- 24 subjects have completed both the prediction and chamber days, and we have been able to predict with ~80% accuracy which subjects will get sick within 10 hrs at 11.5% O_2
- Nuclear imaging techniques refined and set for initiation of data collection.
- Completed data collection for validation of our results in a field study.

8th Quarter Research Accomplishments:

- 3 PFO- and 5 PFO+ subjects completed both the prediction day breathing 14% O_2 for 30 min and the chamber day visit, breathing 11.5% O_2 for 10 hrs.
- Nuclear imaging techniques refined and set for initiation of data collection.
- Completed data collection for validation of our results in a field study.

Reportable Outcomes:

- Using saline contrast echocardiography, bubble score obtained after 15-30 minutes breathing 14% O_2 can predict with ~80% accuracy who will develop AMS during 10 hrs breathing 11.5% O_2.
- Using saline contrast echocardiography to detect the presence and determine the characteristics of a patent foramen ovale predicts that subjects who demonstrate intracardiac shunting without performing a Valsalva maneuver will develop AMS within 10 hrs at 11.5% O_2.
- PFO+ subjects are not more susceptible to AMS unless intracardiac shunting occurs without performing a Valsalva maneuver, in which case, we are able to predict that these individuals are AMS susceptible with 100% accuracy.

Conclusion:

After having 24 subjects breathe 14% O_2 for 30 minutes and detecting intrapulmonary and intracardiac shunt with saline contrast echocardiography we can predict with 80% accuracy that subjects who achieve a bubble score of 3 after breathing 14% O_2 for 15-30 minutes are predicted to be AMS susceptible. **Using saline contrast echocardiography to detect the presence and characteristics of a patent foramen ovale, can predict AMS susceptibility with 100% accuracy if the subjects demonstrates a patent foramen ovale without performing a Valsalva maneuver.**

So what? For years now people have tried, without much success, to implicate the hypoxic ventilatory response in determining individual susceptibility to AMS and have achieved a ~50% rate of success. Alternatively, it is well known that shunt plays a negative role in pulmonary gas exchange efficiency and that decreased gas exchange efficiency is well correlated with AMS susceptibility. What isn't known is who will have the worst gas exchange efficiency and thus the greatest susceptibility to AMS. Our results clearly support the idea that bubble score and/or the presence of an intracardiac shunt such as a PFO can clearly be used to determine who will get sick at high altitude as we can currently predict AMS susceptibility with 80% to 100% certainty, depending on the source of shunt.

References:

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2. **Loeppky JA, Icenogle MV, Charlton GA, Conn CA, Maes D, Riboni K, Gates L, Melo MF, and Roach RC**. Hypoxemia and acute mountain sickness: which comes first? *High Alt Med Biol* 9: 271-279, 2008.

Appendix

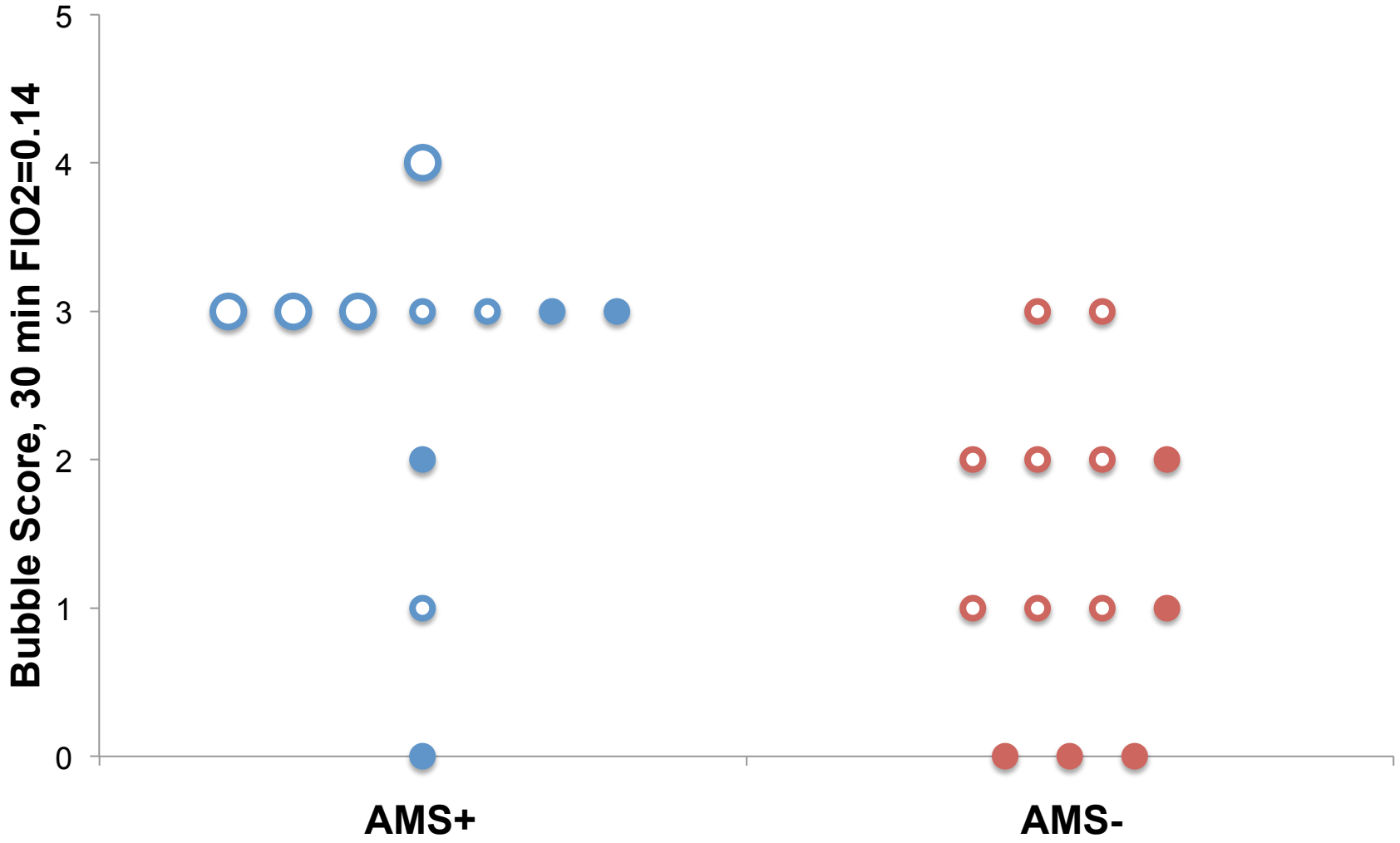

Fig. 1 shows bubble score obtained after breathing a hypoxic gas mixture (FIO_2=0.14) for 30 minutes. Each data point represents 1 subject and subjects are divided by AMS susceptibility; AMS susceptible (AMS+) or AMS resistant (AMS-). PFO+ subjects are indicated by open circles. Small circles=Valsalva induced PFOs, large circles=non-Valsalva PFOs. N=15 PFO+, n=9 PFO-.

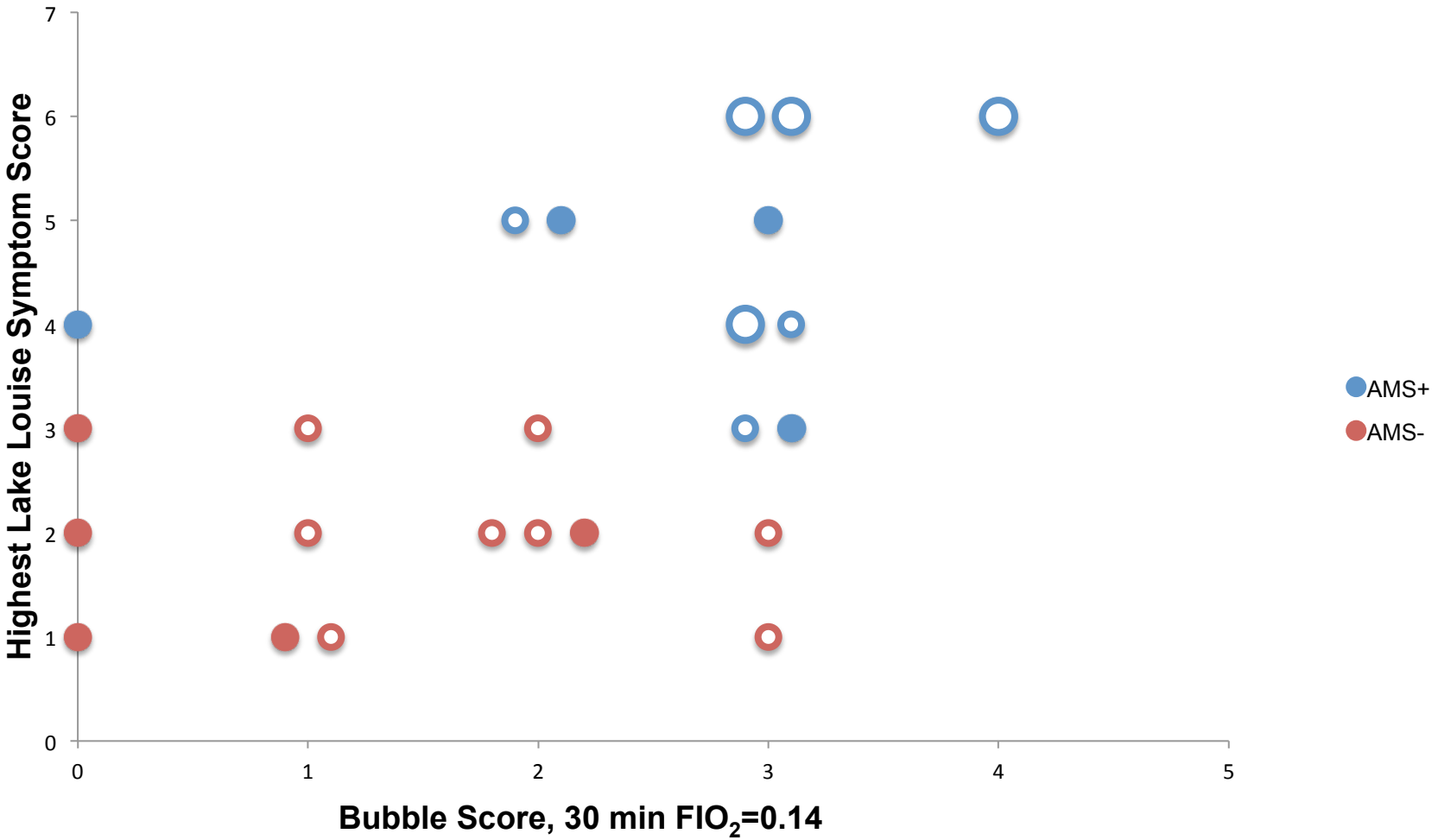

Fig. 2 shows shunt scores obtained after breathing a hypoxic gas mixture (FIO_2=0.14) for 30 minutes vs. the highest Lake Louise Symptom Score achieved over 10 hrs breathing 11.5% O_2 in the chamber, which is ~4,760 m. PFO+ subjects are indicated by open circles. Small circles=Valsalva induced PFOs, large circles=non-Valsalva PFOs. n=15 PFO+, n=9 PFO-.

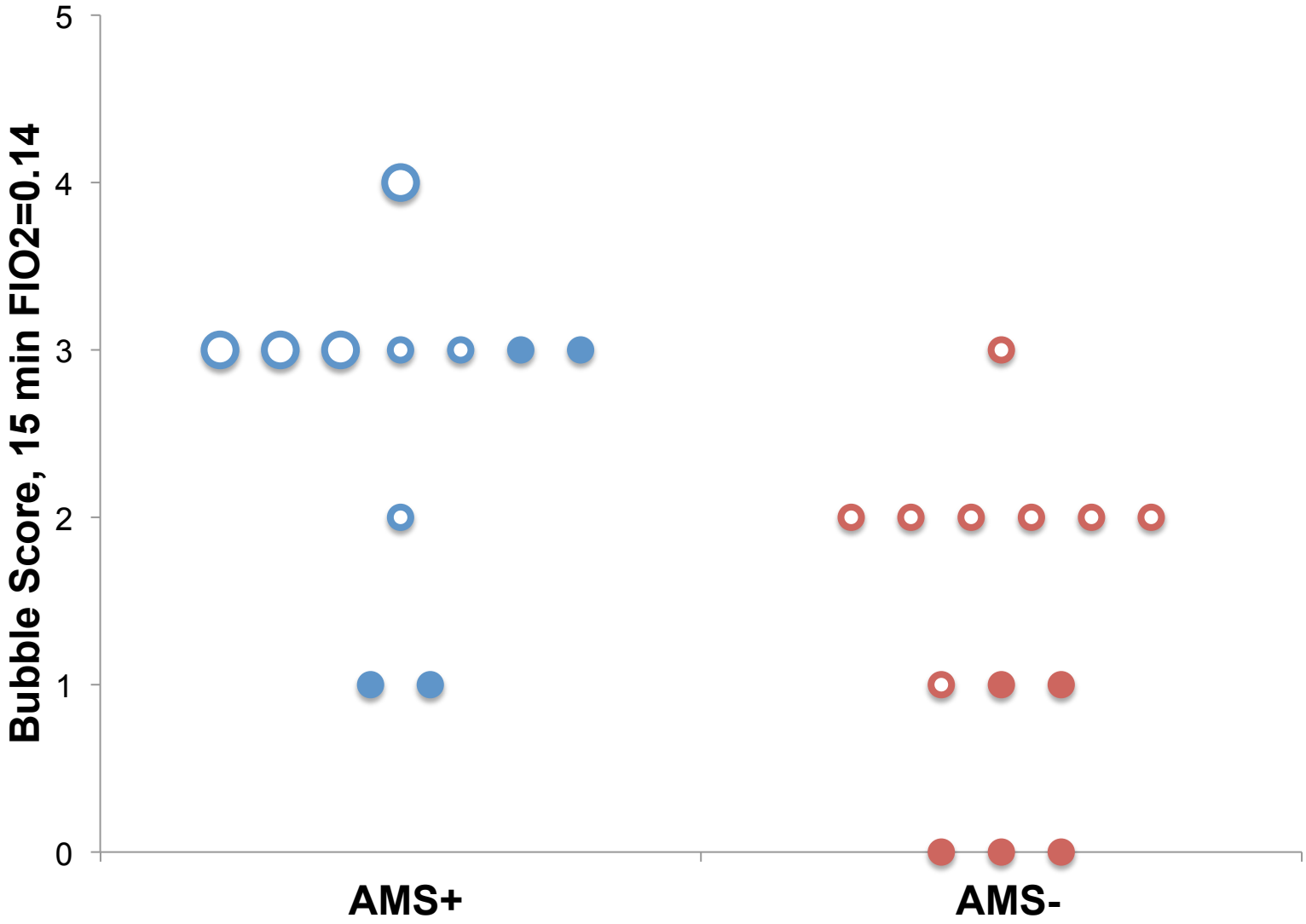

Fig. 3 shows bubble score obtained after breathing a hypoxic gas mixture (FIO_2=0.14) for 15 minutes. Each data point represents 1 subject and subjects are divided by AMS susceptibility; AMS susceptible (AMS+) or AMS resistant (AMS-). PFO+ subjects are indicated by open circles. Small circles=Valsalva induced PFOs, large circles=non-Valsalva PFOs. n=15 PFO+, n=9 PFO-.